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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

		Atty. Docket: TOVEY=1A
In re Application of:	)	Conf. No.: 1869
Michael TOVEY	)	Art Unit: 1614
Appln. No.: 09/243,030	)	Examiner: Jerome Goldberg
Filed: February 3, 1999	)	Washington, D.C.
For: THERAPEUTIC APPLICATIONS OF HIGH DOSE ...	)	September 22, 2003

BRIEF ON APPEAL

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, Mail Stop Brief-Patents
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Submitted herewith is applicant's Brief on Appeal in triplicate.

The present appeal is taken from the examiner in finally rejecting claims 22-51. The full text of claims 22-51 under appeal appears in Appendix A attached hereto.

REAL PARTY IN INTEREST

The present application is owned by Pharma Pacific Pty Ltd which is a corporation of New South Wales, Australia.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

Claims 22-51 presently appear in this case. Claims 1-21 have been canceled.

STATUS OF AMENDMENTS

No amendments to the claims have been filed subsequent to the date of the final rejection of October 18, 2002. A request for reconsideration was filed on January 21, 2003, and in the advisory action of June 13, 2003, the examiner indicated that this request for reconsideration had been considered.

SUMMARY OF THE INVENTION

The present invention relates to a method for the treatment of viral infections by the administration of interferon (see the paragraph bridging pages 31 and 32 of the present specification). The improvement of the present invention concerns the mode of administration and the dose. The interferon is administered via oromucosal contact, which means administration of the interferon preparation by means of distribution into the oromucosal cavity, i.e., the mouth and throat of the recipient mammal, so as to make contact with the

mucosa lining this cavity (page 17, lines 16-22, and page 12, lines 11-19). The dose is a high dose which is greater than 20 × 10^6 IU of interferon for a 70kg human, preferably greater than 30 × 10^6 IU of interferon, which dose is in excess of a dose of the same interferon which induces a pathological response when parenterally administered (paragraph bridging pages 13 and 14 of the present specification; page 8, lines 13-14 and page 8, lines 16-20). The oromucosal administration is conducted in a manner which does not involve direct action of the interferon on virally infected cells (page 34, line 15).

In one specific embodiment of the invention, when the viral infection is a rhinoviral infection, the interferon is not administered in a multiple or continuous dose, except that it may be administered intranasally by multiple or continuous dose. Rhinovirus is disclosed at page 10, line 25. Nasal administration is disclosed at page 12, line 15. Administration by multiple or continuous dosages is described at page 12, lines 21-25. Administration in a single dose which is not a multiple or continuous dose is described at page 12, line 20.

The effects of the present invention are surprising, as tests described in the specification disclose that biologically active interferon does not enter the blood stream following oromucosal administration (see example 6, beginning at page 25, and example 7, beginning at page 28; see also page 34, lines 16-

17). It appears that the mechanism of the present invention may act at least partly by stimulation of the abundant lymphoid tissue surrounding the nasopharyngeal and oral cavities (page 34, lines 17-19). The oromucosally administered interferon is at least comparable in efficacy to systemically administered interferon (page 34, lines 19-20), despite the fact that it does not enter the blood stream in biologically active form.

THE PRIOR ART

The following prior art was relied upon by the examiner in the final rejection of October 18, 2002:

Canadian patent 1,297,788

U.S. patent 5,286,748, Eby, III

The Canadian patent discloses a method for the treatment of patients infected with the virus that causes AIDS by the administration of high doses of recombinant alpha interferon. The high doses can range from about 5-75 $\times$ 10^6 IU of human recombinant interferon α-2 per day by single injection. In the paragraph bridging pages 3 and 4, the Canadian patent states that the interferon is administered by injection and at page 4, line 30, it states that the administration is accomplished parenterally. At page 6, lines 4-7, it states that the preferred mode of administration is by subcutaneous injection. Thus, the Canadian patent is directed to treating only a single type of virus (HIV) by a very specific mode of administration

(parenteral, preferably subcutaneous injection). There is no suggestion of any mode of administration other than parenteral or the treatment of any virus other than HIV.

Eby III is also directed to treating a specific type of virus by a very specific mode of administration. Eby III is directed to the treatment of "acute viral infections of the nose usually caused by rhinoviruses" (column 1, lines 52-53). Eby III states, at column 3, lines 24-33:

> Since zinc gluconate works in the oral cavity but not in the nose, this inventor believes and teaches that all suitable common cold medicaments such as antiviral agents, antirhinoviral agents, interferon, interferon inducers, T-cell lymphocyte mitogens, decongestant, drying agents, astringents, antihistamines, antibradikinins, and all other pharmaceutical agents suitable for treating common colds will have efficacy, or greater efficacy, when applied to the oral mucosa than when applied to the inside of the nose, injected or swallowed.

Thus, the Eby III disclosure is not directed to an improved mode of administration of interferon. It is only directed to an improved mode of administration of a common cold medicament, of which interferon is only one of a long list of possible medicaments.

Eby III also teaches the reason why it is desired to apply to the oral mucosa when treating a rhinovirus infection, where it states in the second paragraph of column 4:

> Application of antiviral agents including antirhinoviral agents to the oral mucosa through the incorporation of said antiviral agents within a slow release lozenge or other similar oral means presents a new method of adminisration that has the potential to inject said medicament into the lymphatic system or otherwise to circulate into the nasal tissue and the locus of infection. Although the means by which zinc ion are transported into nasal tissues in the original demonstration of this technique is not known but is suspected to involve diffusion, osmosis and electrophoresis and drainage by the lymphatic system, it is suggested that the same means of transport would also apply to other antiviral agents.

In the following paragraph Eby III states that all methods directed at reducing the duration of common colds through means of administering antiviral agents by swallowing, injection or by administration to the nose have proven unsatisfactory.

Eby III contains no suggestion that the mode of administration taught therein for the treatment of the common cold would be applicable to the treatment of any other virus, let alone HIV.

THE REJECTIONS

In the final rejection of October 18, 2002, claims 22-51 were rejected under 35 USC 103(a) as being unpatentable over the Canadian patent 1,297,788, taken with Eby III, the examiner stating:

> The Canadian patent teaches the application of interferon at 5 to 75 million international

> units for treating the virus causing AIDS. Applicant's claims are directed to greater than 30 x 10^6 IU of interferon by oromucosal contact. The Eby III patent teaches the application of interferon by oral mucosa to treat other viral infections. The primary reference does not teach the oral mucosa administration. Accordingly, one skilled in the art would find ample motivation from the prior art supra to employ the interferon by oral mucosa with a reasonable expectation that said interferon would be effecting [sic] to combat said viral infection in the absence of w [sic] showing of oral mucosa us injectable form for the high dosages disclosed.

In the Advisory Action of June 13, 2003, the examiner stated:

> The request for reconsideration has been considered but does NOT place the application in condition for allowance because: the instant claim 33 is directed to a Makush group containing both HIV and rhinovirus infections.

ISSUES

The following issue is presented in this appeal:

Would the present invention have been obvious at the time the invention was made to a person of ordinary skill in the art having knowledge of the Canadian patent and Eby III.

GROUPING OF CLAIMS

All of the present claims stand or fall together.

A R G U M E N T

The examiner has provided no evidence that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention

It is well established that an examiner must show that there was motivation for one of ordinary skill in the art to combine the references in the manner suggested by the examiner before a *prima facie* case of obviousness has been established. Note particularly *Ex parte Levengood*, 28 USPQ 2d 1300, 1301 (Bd. Pat. App. Int. 1993), where it states:

> In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. [emphasis original; footnote omitted]

Here, there is no teaching, suggestion, incentive or inference in either the Canadian patent or Eby III that would have led one of ordinary skill in the art to combine the teachings thereof to arrive at the present invention.

As discussed above in the discussion of the prior art, the primary reference, i.e., Canadian patent number 1,297,788 discloses only the treatment of the AIDS virus with recombinant human alpha interferon administered parenterally, preferably by

subcutaneous injection. The examiner recognizes that the Canadian patent does not teach oromucosal administration for the treatment of AIDS. However, the examiner contends that one of ordinary skill in the art would have found ample motivation from Eby III to administer the interferon oromucosally with a reasonable expectation that such interferon would be effective to combat the virus that causes AIDS. But to the contrary, anyone of ordinary skill in the art giving a fair reading to Eby III would never have considered applying any of its teachings to any process for the treatment of AIDS.

Eby III is directed only to the treatment of acute viral infections of the nose, usually caused by rhinoviruses. The patent is directed to the oromucosal administration of any medicament suitable for the treatment of the common cold, such as "antiviral agents, antirhinoviral agents, interferon, interferon inducers, T-cell lymphocyte mitogens, decongestant, drying agents, astringents, antihistamines, antibradikinins, and all other pharmaceutical agents suitable for treating common colds" (column 3, lines 26-32). Thus, interferon is only one of a long list of possible agents which can be used in the process of Eby III for the treatment of the common cold. Eby III discloses that if any of these medicaments is administered oromucosally, it will have a greater efficacy in treating the common cold than when applied directly to the nasal tissues, injecting or orally administering by swallowing (column 3, lines 35-41 of Eby).

Thus, Eby III is not directed to an improved mode of administration of interferon, it is only directed to an improved mode of administration of a common cold medicament, of which interferon is only one of a long list of possible medicaments.

The reason given by Eby III for administering oromucosally is that the medicament thereby enters the lymphatic system, or otherwise circulates into the nasal tissue and the locus of infection (column 4, lines 9-15).

What then is the motivation of one of ordinary skill in the art to combine the teachings of Eby III with the Canadian patent? Eby III is directed only to the treatment of the common cold and states that the oromucosal administration works well because it directs interferon into the locus of infection. In AIDS, the locus of infection is not the nasal tissue, and therefore there would be no reason for one of ordinary skill in the art to consider using the mode of administration disclosed for rhinoviruses in Eby III.

Furthermore, the Canadian patent is directed only to the administration of interferon. Eby III is directed to the administration of any pharmaceutical suitable for treating common colds, of which interferon is one of a long list. There is no reason for one of ordinary skill in the art reading Eby III to believe that this teaching which is specific for cold remedies, including interferon, would be applicable to a method of treating a totally different indication, which is not normally treated

with cold remedies, and in which the oromucosal administration of medicament would not provide any direct contact with the locus of infection.

In the advisory action, the examiner disregarded applicant's arguments because "the instant claim 33 is directed to a Markush group containing both HIV and rhinovirus infections." However, this statement is irrelevant to the issue of motivation. The fact that the present claims disclose that the present invention is applicable both to rhinovirus and to HIV is irrelevant to what the Canadian patent and Eby III would have taught to one of ordinary skill in the art at the time the present invention was made. The present claims are not part of the prior art. The fact is that the Canadian patent is limited only to the treatment of HIV, while the Eby III patent is limited only to the treatment of rhinovirus. As discussed above, there is no motivation to use the means of administration disclosed by Eby III for the treatment of rhinovirus, in the treatment of AIDS taught by the Canadian patent. This is particularly so in light of the teaching of Eby III that the mode of administration disclosed therein is applicable to any pharmaceutical agent suitable for treating the common cold and its effectiveness is based on causing the agent to circulate into the locus of infection.

Accordingly, no combination of the Canadian patent and Eby III would have provided motivation to one of ordinary skill

in the art at the time the present invention was made to administer the alpha interferon of the Canadian patent oromucosally for the treatment of the virus which causes AIDS. Reversal of the examiner and withdrawal of this rejection is therefore respectfully urged.

CONCLUSION

The claims as submitted are believed to fully define over the references of record. Accordingly, reversal of the examiner and allowance of claims 22-51 are earnestly solicited.

Respectfully submitted,

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APPENDIX A

22. The method of claim 37 in which the effective dose of interferon is administered in a single dose.

23. The method of claim 37, in which the effective dose of interferon is administered in a plurality of smaller doses over a period of time sufficient to elicit a response equivalent to that of a single dose.

24. The method of claim 37, in which an effective dose of interferon is administered continuously over a period of time sufficient to elicit a response equivalent to that of a single dose.

25. The method of claim 37, wherein the interferon comprises a Type I interferon.

28. The method of claim 37, wherein the interferon comprises a Type II interferon.

30. The method of claim 37, wherein the dose of interferon is up to about 1000×10^6 IU of interferon.

31. The method of claim 37, wherein the dose of interferon is up to about 500×10^6 IU of interferon.

32. The method of claim 37, wherein the dose of interferon is from about 50×10^6 IU to about 500×10^6 IU of interferon.

33. The method of claim 37, wherein the viral infection is selected from the group consisting of rhinovirus, influenza, herpes varicella, herpes zoster, dengue fever, viral encephalitis, haemorrhagic fever, genital herpes, equine morbillivirus, hepatitis B, hepatitis C, hepatitis D, CMV, HIV, HPV, HSV- I and HSV-2.

34. The method of claim 33, wherein said viral encephalitis is selected from the group consisting of measles virus encephalitis, Murray Valley encephalitis, Japanese B encephalitis, tick-borne encephalitis and Herpes encephalitis.

35. The method of claim 33, wherein said haemorrhagic fever is selected from the group consisting of Ebola virus, Marburg virus, Lassa fever, and Hanta virus infections.

36. A method for treating a viral infection, which method comprises administering to the mammal having such a viral infection an effective amount of greater than about 20×10^6 IU of interferon for a 70 kg human via oromucosal contact, said amount being in excess of a dose of the same interferon which induces a pathological response when parenterally administered, said oromucosal administration being in a manner which does not involve direct action of the interferon on virally infected cells and provided that when the viral infection is a rhinoviral infection, the interferon is not

administered in a multiple or continuous dose or is administered intranasally by multiple or continuous dose.

37. A method for treating a viral infection, which method comprises administering to the mammal having such a viral infection greater than about 30×10^6 IU of an interferon via oromucosal contact, said amount being in excess of a dose of the same interferon which induces a pathological response when parenterally administered, said oromucosal administration being in a manner which does not involve direct action of the interferon on virally infected cells.

38. The method of claim 36 in which the effective dose of interferon is administered in a single dose which is not a multiple or continuous dose.

39. The method of claim 36, in which the effective dose of interferon is administered intranasally, in a plurality of smaller doses over a period of time sufficient to elicit a response equivalent to that of a single dose.

40. The method of claim 36, in which an effective dose of interferon is administered intranasally continuously over a period of time sufficient to elicit a response equivalent to that of a single dose.

41. The method of claim 36, wherein the interferon comprises a Type I interferon.

42. The method of claim 41, wherein the interferon is selected from the group consisting of IFN-α, IFN-β, IFN-ω, consensus IFN, and mixtures thereof.

43. The method of claim 42, wherein the IFN-α comprises recombinant IFN-α.

44. The method of claim 36, wherein the interferon comprises a Type II interferon.

45. The method of claim 44, wherein the Type II interferon comprises IFN-γ.

46. The method of claim 36, wherein the dose of interferon is up to about 1000×10^6 IU of interferon.

47. The method of claim 36, wherein the dose of interferon is from up to about 500×10^6 IU of interferon.

48. The method of claim 36, wherein the dose of interferon is from about 50×10^6 IU to about 500×10^6 IU of interferon.

49. The method of claim 36, wherein the viral infection is selected from the group consisting of rhinovirus, influenza, herpes varicella, herpes zoster, dengue fever, viral encephalitis, haemorrhagic fever, genital herpes, equine morbillivirus, hepatitis B, hepatitis C, hepatitis D, CMV, HIV, HPV, HSV- I and HSV-2.

50. The method of claim 49, wherein said viral encephalitis is selected from the group consisting of measles

virus encephalitis, Murray Valley encephalitis, Japanese B encephalitis, tick-borne encephalitis and Herpes encephalitis.

51. The method of claim 49, wherein said haemorrhagic fever is selected from the group consisting of Ebola virus, Marburg virus, Lassa fever, and Hanta virus infections.